Sipuleucel-T Pharmacovigilance Issues Brief

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Sipuleucel-T (antigen loaded autologous antigen presenting cells)
Immunotherapy of Prostate Cancer
Dendreon Corporation

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I. Epidemiology

Prostate cancer is the most common solid tumor malignancy in men in the U.S. It is expected to account for over 192,280 new cases and 27,360 deaths in 2009 (American Cancer Society 07/09). While primary therapies of surgery and radiation usually control the disease, approximately 20-40% of patients eventually experience recurrence. For those in whom disease recurs, androgen deprivation is the standard treatment, resulting in temporary tumor control in 80-85%. Most patients then become refractory to hormone therapy, when they are known as "castrate resistant." Almost all such patients die of their disease, because no good current treatment options are available for this stage.

II. Product

Sipuleucel-T (APC8015) is an autologous, active cellular immunotherapy product designed to stimulate an immune response against prostate cancer. The proposed indication is treatment of men with metastatic castrate resistant (hormone refractory) prostate cancer. Castrate resistant prostate cancer (CRPC) describes patients who have progressive disease while on hormone therapy.

The composition of sipuleucel-T depends on the composition of cells obtained from a patient's own leukapheresis. Each dose of sipuleucel-T contains autologous mononuclear cells, including antigen presenting cells, that were activated ex vivo via culture with a recombinant fusion

protein consisting of prostatic acid phosphatase (PAP) linked to granulocyte-macrophage colony-stimulating factor (GM-CSF), an immune cell activator. The recommended course of therapy for sipuleucel-T is 3 doses, given at approximately 2-week intervals by intravenous infusion. Each dose is preceded by a standard leukapheresis procedure approximately 2-3 days in advance. Each batch is prepared for and administered to only one patient.

The investigational New Drug (IND) application (BB-IND 6933) for sipuleucel-T was first submitted in November 1996. Since that time, 11 clinical Phase 1, 2, and 3 studies have been completed in men with prostate cancer. In addition, 3 subjects were treated on a compassionate use basis. Safety data are available for all 11 clinical studies and for 2 of the 3 compassionate use subjects.

III. Demographics

The demographic characteristics were similar between the sipuleucel-T and placebo groups for the four Phase 3 studies presented in the Integrated Safety Assessment. The subjects were all male, 90.6% were Caucasian, and their median age was 70 years. The median time from diagnosis of prostate cancer to randomization was 6.5 years.

IV. Analysis of Adverse Events

Safety information presented in this review comes from the Integrated Summary of Safety (ISS) submitted on Oct 30, 2009. Safety data includes summarized data for the 4 integrated Phase 3 randomized, double-blind, placebo controlled studies D9902B, D9901, D9902A and P-11. *Inclusion of P-11 allows for a larger safety database to analyze rare and less common AE's, such as cerebrovascular events.*

Serious adverse events (SAEs) include any adverse drug experience that results in death, life-threatening adverse drug experience, inpatient hospitalization, or persistent or significant disability. All AE's from studies D9901, D9902A, D9902B (through the cut off of 18 Jan 2009), and P-11 (through 23 Jan 2009) were included in the integrated analysis.

In all 11 clinical studies, a total of 1010 subjects received either sipuleucel-T (n=693), placebo alone (137), placebo followed by APC8015 (n=165), or APC8026 (n=15). (Note: APC8015 and APC8026 are different formulations of the product with a similar method of manufacture and composition and are, thus, included in the safety analysis.) Overall, 531 of the 1010 subjects have been reported to have died across all studies. Given that the median life expectancy for men with CRPC is less than 2 years, death is an expected outcome.

Of the 904 subjects (601 randomized to sipuleucel-T and 303 randomized to placebo) in the four ISS studies (D9902B, D9901, D9902A, and P-11), 56.1% of subjects died as of the data cut-off. Of the fatalities, 53.2% of subjects were in the sipuleucel-T group and 61.7% of the subjects were in the placebo group. The majority of deaths were attributed to disease progression**.**

A review of cause of death where "other" was selected was performed by the sponsor. Study D9902B allowed more than 1 cause of death to be selected. In the **sipuleucel-T group,** more than one diagnosis could be recorded as cause of death. 5 subjects died of CVE, 2 each of

congestive heart failure (CHF), subdural hematoma, sepsis, esophageal cancer and 1 each of urinary tract infection (UTI), dementia, renal failure, leukemia, glioblastoma, suicide, cardiac arrest, brain aneurysm, and intracranial bleeding. In the placebo group, 11 patients had a cause of death identified as "other." 2 subjects died of CHF, 1 each of CVE, lung cancer, aspiration, colitis, sepsis, scleroderma and respiratory failure.

A total of 882 of the 904 subjects in the four ISS studies (97.6%) reported AEs. The most commonly reported AE's occurring in >5% of subjects and observed at least twice as frequently as in the placebo group included chills, fatigue, pyrexia, headache, myalgia, flu like symptoms, hyperhidrosis. These AE's generally occurred within 1 day of infusion and were of short duration. Overall, 24.3% of subjects in the safety population (220 of 904) developed an SAE, 24.0% of subjects (144 of 601 subjects) in the sipuleucel-T group and 25.1% of subjects (76 of 303 subjects) in the placebo group. The System Organ Class (SOC) of Nervous System Disorders indicated that 5.8% of subjects (35 of 601 subjects) in the sipuleucel-T group experienced SAEs compared with 3.3% of subjects (10 of 303 subjects) in the placebo group. The majority of these events in both treatment groups were due to cerebrovascular events (CVEs) and transient ischemic attacks (TIAs).

Cerebrovascular Events

An important potential risk associated with sipuleucel-T is the occurrence of CVEs. A review of safety information after Dendreon's 3 initial Phase 3 trials (D9902B, D9901, and D9902A) had revealed a possible increase in the incidence of CVE in the sipuleucel-T group. All types of CVEs, (e.g., hemorrhagic, ischemic, TIA, and bleeding from dural metastatic lesion) were included in this previous analysis. The sources of data reviewed for that analysis included AEs and SAEs collected per the clinical trial protocol (regardless of attribution for relatedness), as well as cause of death information as determined by the investigator. Similar analyses were performed for the data presented here (includes Studies D9902B, D9901, D9902A, and P-11) with the exception that TIAs were not included because they do not have the same persistent clinical consequences of other CVEs.

In the four ISS trials, 766 patients received treatment with Sipuleucel-T (includes APC8015F) and 303 received placebo. Among these, 2.9% of sipuleucel-T treated subjects (22 of 766) experienced a CVE (incidence rate per 100 person-years=1.74 (95% CI: 1.09, 2.63)), and 2.3% of placebo treated subjects (7 of 303) experienced a CVE (incidence rate per 100 person-years=1.86 (95% CI: 0.75, 3.83)). Including TIA events, 3.3% of sipuleucel-T treated subjects (25 of 766) experienced a CVE (incidence rate per 100 person-years of 1.98 (95% CI: 1.28, 2.93)), and 2.6% of placebo treated subjects (8 of 303) experienced a CVE (incidence rate per 100 person-years= 2.13 (95% CI: 0.92, 4.20)).

Of the subjects who experienced CVE in the four Phase III trials, 38.1% of subjects randomized to sipuleucel-T had a fatal event compared to 25.0% of subjects randomized to placebo. In the sipuleucel-T group, 1.4% of subjects experienced fatal CVE (the incidence rate=0.763 per 100 person-years (95% CI: 0.329, 1.503)) and, in the placebo group, 0.7% of subjects experienced fatal CVE (incidence rate=0.370 per 100 person-years (95% CI: 0.045, 1.337)).

A review of CVE's based on history of prior CVE revealed 3 subjects with a history of prior CVE, and all 3 were randomized to the sipuleucel-T group. Excluding subjects with a history of

CVE prior to treatment, the rate of CVE was comparable between the 2 arms: 18 of 577 (3.1%) in the sipuleucel-T group compared to 8 of 291 (2.8%) in the placebo group.

Cerebrovascular event analyses were performed for the 3 initial Phase III studies (Studies D9902B, D9901 and D9902A only) excluding TIA. In these 3 studies, 19 of 650 subjects in the treatment group (2.92%) and 4 of 244 placebo subjects (1.64%) experienced CVEs. The incidence rate per 100 person-years for subjects treated with sipuleucel-T was 2.13 (1.28, 3.33) and for subjects treated with placebo was 2.38 (0.65, 6.09). The sponsor concluded that the CVE incidence rate per 100 person years was similar between the 2 treatment groups, and the rates were consistent with those observed in a SEER-Medicare database.

V. Safety concerns

- A higher incidence of CVEs was noted in sipuleucel-T treated patients compared to placebo (although not statistically significant).

VII. Postmarketing Data

Sipuleucel-T is not marketed in the United States or any other country.

VIII. Pharmacovigilance plans proposed

In addition to routine monitoring and reporting of spontaneously reported adverse events, Dendreon proposes the following Pharmacovigilance activities to monitor the post-approval use and safety of sipuleucel-T in patients with metastatic castrate resistant prostate cancer.

Sipuceucel-T pharmacovigilance will be enhanced by stringent control over production and distribution of the product. There will be a direct link to all infusion and apheresis centers involved.

- *This enables knowledge of the exact denominator data.*
- *Each patient is connected with a specific lot number.*
- *Direct communication with each prescribing physician*
- *Contact information for every prescriber*

Dendreon proposes to conduct a Registry study with a target enrollment of 1,500 subjects to further quantify the adverse events and survival time in the treated population. The sponsor calculates that this sample size is adequate to provide 80% power to detect a rare adverse event (1:1,000). Data collection will continue until every patient has died or has been followed for at least 3 years. Depending on the length of the accrual period, the total duration of data collection is expected to be approximately 6 years.

Registry Protocol Title: A Single Arm, Multi-Center, Observational Safety and Survival Follow-Up Registry for Sipuleucel-T Therapy in Men with Metastatic Castrate Resistant Prostate Cancer. Registry will be strictly observational. Physicians will record information as it becomes available through structured data management process. Following the last infusion, patients will be followed for safety and survival. Survival status will be obtained by the registry site every 3-6 months until every patient has been followed for a minimum of 3 years. Data on treatment related adverse events and cerebrovascular events will be collected. Baseline information

including demographics, disease status, medical history, and prognostic factors will be collected.

The biology and prognosis of prostate cancer and cardiovascular disease may be different in African American vs. Caucasian populations, and the number of African-Americans studied in the clinical trials to date for sipuleucel-T is not adequate to fully define the safety profile in this population. Dendreon proposes to include at least 200 African Americansin the registry population.

The sponsor's stated objectives for the registry are to:

1. further quantify the risk of serious adverse events following sipuleucel-T therapy.
2. quantify survival time and adverse events for African American patients in comparison with non African American patients.

IX. Assessment and Recommendation:

1. A higher percentage of sipuleucel-T treated subjects experienced CVEs as compared to placebo. This safety signal warrants a post-market requirement (PMR) for a study to further evaluate CVE risk in sipuleucel-T treated subjects. A review of safety information after Dendreon's 3 initial Phase 3 randomized trials (D9902B, D9901, and D9902A) had revealed a possible increase in CVEs in the sipuleucel-T (2.92%) vs. the placebo group (1.64%). In the more recent analysis including all four of Dendreon's phase III trials, there is less difference between the treatment (2.9%) and placebo groups (2.3%). However, these additional data do not provide sufficient evidence to exclude the possibility that sipuleucel-T may raise the CVE risk in treated patients.

2. Pertinent Section of FDAAA

If sipuleucel-T is approved, the sponsor should be required to conduct a study as a PMR to assess CVE risk. Under the FDA Amendments Act (FDAAA), section 505(o)(3)(B)(iii), FDA has the authority to require studies or clinical trials based on scientific data:

- to assess a known serious risk related to the use of the drug involved;
- to assess signals of serious risk related to the use of the drug; or
- to identify an unexpected serious risk when available data indicates the potential for a serious risk.

3. Rationale for Recommending PMR

Based on the safety data presented to date, the adverse event of CVE in sipuleucel-T treated clinical trial subjects represents a signal of a serious risk as defined under FDAAA.

In the guidance document on *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment,* the FDA defines a safety signal to be a "concern about an excess of adverse events

compared to what would be expected to be associated with a product's use." This definition of signal is broad and allows for a range of levels of concern based on: Strength of the association (e.g., relative risk in a controlled study), temporal relationship of product and event, consistency of findings across available data, evidence of dose response effect, biologic plausibility, and the susceptibility of the methods used to confounding, bias, and chance. Levels of concern can range from low (an unexpected serious AE in the setting of substantial methodological limitations in data or study design); to high (an unexpected serious AE with statistically significant increased relative risk and few limitations in data or study design). Identifying the level of concern helps to establish what actions are required, with lower levels of concern typically handled by postmarketing surveillance and studies. In contrast, higher levels of concern might require additional studies before a product is marketed.

Using this framework, the relatively low CVE incidence rates represent a weak signal of a serious risk. Only a small number of CVE cases were observed in both the treatment and placebo groups, representing a low strength of association. However, the guidance notes that even a single well-documented case can be viewed as a signal. In the initial Phase 3 studies and in the more recent ISS analysis of all 4 phase III studies to date, CVE occurred in a higher percentage of subjects in the treatment group than the placebo group.

When analyzed by person-years, CVE rates per 100 person-years tended to be higher in the placebo group (1.86 per 100 person-years (95% CI: 0.75, 3.83) than the treatment group (1.74 (95% CI: 1.09, 2.63)), and the difference between the groups was not statistically significant. However, occurrence of CVE was not an *a priori* endpoint in these studies, and they were not sized or designed for its evaluation. In addition, differences in survival time between the two groups may have led to a censoring bias in placebo subjects when examining by person-years. Because their follow- up time was shorter than treated patients due to their earlier mortality, placebo subjects were, in effect, censored. The incidence per person-years in placebo subjects might appear high because of the small denominator (due to the shorter length of follow-up time). In contrast, the survival of treated subjects was longer, and the incidence per person-years in this group might appear lower because of the relatively larger denominator (due to longer follow up time). Last, the relatively small size of the clinical trial population limits our ability to conclude that these cases do not represent an excess over the expected background rate in this kind of clinical population.

CVEs are a known complication of malignancy in general, and it is difficult to definitely attribute the occurrence of this AE to the treatment versus the relatively high background risk in this population. Many of the patients experiencing CVE had a prior history of similar events. Excluding these patients, the incidence of CVE in the treatment group was more similar to the placebo group (3.1% in the sipuleucel-T group compared to 2.8% in the placebo group) but was still higher in treated subjects. Further, sipuleucel-T may have also contributed to CVE recurrence in patients with a history of this event. Because CVE risk appeared to be higher in treated patients among the complete study population, as well as those without CVE history, CVE represents a safety signal for all treated patients. Additional study of the risk of CVE in those with and without history of CVE will help to further clarify the importance of prior CVE as a risk factor in treated patients.

Several features of these events are consistent with a signal as defined in the guidance:

- The pharmacological/toxicological effects of antigen-pulsed autologous cells, including the risk of CVE, have not been fully established. The pharmacologic/toxicological effects of products in this class are unknown, since this is a novel cellular immunotherapy. Adverse events that might occur in relation to treatment with sipuleucel-T, including its potential for thrombogenicity, are not fully understood.
- The CVEs occurred within an appropriate timeframe after treatment to reasonably be associated with the product.

Thus, CVEs represent a signal of a serious risk with a relatively low level of concern (i.e., a weak signal). Under FDAAA, this signal can be considered a scientific basis for a PMR to study CVE risk. This study should collect additional data on the risk of CVE in treated subjects with and without a history of CVE.

4. PMR Planning

The sponsor should submit a detailed protocol for a study of CVE risk to fulfill this requirement. If the sponsor elects to do so, the proposed registry study might fulfill this requirement. If so, the sponsor should develop an analysis and reporting plan for using the registry to assess CVEs, including an assessment of the proposed sample size specifically for the ability to detect an excess of CVEs in sipuleucel-T treated patients when compared to the background CVE incidence in a similar population.